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group consisting of SEQ ID NOS: 2, 3, 4, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 24.

6. The method according to claim 5, wherein the cancer is selected from the group consisting of osteosarcoma, soft tissue sarcoma, breast cancer, ovarian cancer, cervical cancer, oral squamous cell carcinoma, brain tumor, esophageal cancer, colorectal carcinoma, bladder cancer, urithelial carcinoma, leukemia, and large B cell lymphoma.
7. The method according to claim 5 comprising co-administering an effective cancer-treating amount of a cancer chemotherapeutic agent.
8. The method according to claim 7, wherein the cancer chemotherapeutic agent is 10-hydorxycamptothecin, adriamycin, or 5-fluorouracil.
9. The method according to claim 5 comprising co-treating the mammal with anti-cancer levels of radiation.
10. (Presently Amended) A method of increasing p53 concentration, the method comprising administering to the cell or to an animal comprising the cell an effective MDM2-expression inhibiting amount of an anti-MDM2 antisense oligonucleotide, wherein said antisense oligonucleotide comprises from about 8 to about 50 nucleotides that inhibits MDM2 protein expression, said oligonucleotide binding to mdm2-encoding RNA and being complementary to a sequence that overlaps by at least one nucleotide a sequence within the mdm2 RNA, which sequence within the mdm2 RNA is selected from the group consisting of SEQ ID NOS: 2, 3, 4, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 24.
11. The method according to claim 10 comprising co-administering a cancer chemotherapeutic agent.
12. The method according to claim 11, wherein the cancer chemotherapeutic agent is 10-hydorxycamptothecin, adriamycin, or 5-fluorouracil.

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13. The method according to claim 10 comprising co-treating the mammal with anti-cancer levels of radiation.
14. (Cancelled Herewith) ~~The method according to claim 1, 2, 4, 5, 6, 7, 9, 10, 11, or 13, wherein the antisense oligonucleotide binds to MDM2 encoding mRNA is complementary to a sequence that overlaps by at least one nucleotide a sequence within the MDM2 RNA, which sequence within the MDM2 RNA is selected from the group consisting of SEQ ID NOS:2, 3, 4, 7, 8, 9, and 11, and wherein the antisense oligonucleotide comprises from about 8 to about 50 nucleotides.~~
15. (Cancelled Herewith) ~~The method according to claim 1, 2, 4, 5, 6, 7, 9, 10, 11, or 13, wherein the antisense oligonucleotide binds to MDM2 encoding mRNA is complementary to a sequence that overlaps by at least one nucleotide a sequence within the MDM2 RNA, which sequence within the MDM2 RNA is selected from the group consisting of SEQ ID NOS:13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 24, and wherein the antisense oligonucleotide comprises from about 8 to about 50 nucleotides.~~
16. (Presently Amended) The method according to ~~claim 14~~ claims 1, 5 or 10, wherein the antisense oligonucleotide has a nucleotide base sequence as set forth in Sequence Listing as SEQ ID NO:28.
17. (Presently Amended) The method according to ~~claim 15~~ claims 1, 5 or 10, wherein the antisense oligonucleotide has a nucleotide base sequence set forth in Sequence Listing as SEQ ID NO:36.
18. (Presently Amended) The method according to ~~claim 14~~ claims 1, 5 or 10, wherein the antisense oligonucleotide has a nucleotide base sequence set forth in Sequence Listing as SEQ ID NO:27, 28, 29, 30, 31, 32, 33, and 34.
19. (Presently Amended) The method according to ~~claim 14~~ claims 1, 5 or 10, wherein the antisense oligonucleotide has a nucleotide base sequence set forth

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- in Sequence Listing as SEQ ID NO:35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, and 46.
20. (Presently Amended) The ~~oligo-nucleotide~~ method according to ~~claim 14~~ claims 1, 5 or 10, wherein the oligonucleotide has at least one internucleotide linkage selected from the group consisting of phosphorothioate, phosphorodithioate, alkylphosphonate, alkylphosphonothioate, phosphotriester, phosphoramidate, siloxane, carbonate, carboxymethylester, acetamidate, carbamate, thioether, bridged phosphoramidate, bridged methylene phosphonate, bridged phosphorothioate, and sulfone internucleotide linkages.
21. (Cancelled Herewith) ~~The oligo-nucleotide according to claim 15, wherein the oligonucleotide has at least one internucleotide linkage selected from the group consisting of phosphorothioate, phosphorodithioate, alkylphosphonate, alkylphosphonothioate, phosphotriester, phosphoramidate, siloxane, carbonate, carboxymethylester, acetamidate, carbamate, thioether, bridged phosphoramidate, bridged methylene phosphonate, bridged phosphorothioate, and sulfone internucleotide linkages.~~
22. The method according to claim 20, wherein the antisense oligonucleotide comprises an RNase H activating segment of four or more consecutive phosphodiester and/or phosphorothioate internucleotide linkages.
23. (Cancelled Herewith) ~~The method according to claim 21, wherein the antisense oligonucleotide comprises an RNase H activating segment of four or more consecutive phosphodiester and/or phosphorothioate internucleotide linkages.~~
24. The method according to claim 22, wherein RNase H activating segment is flanked on both sides by a segment of two or more nucleotides that are modified to increase nuclease resistance and/or target hybridization affinity.

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25. (Cancelled Herewith) ~~The method according to claim 23, wherein the RNase H activating segment is flanked on both sides by a segment of two or more nucleotides that are modified to increase nuclease resistance and/or target hybridization affinity.~~
26. The method according to claim 24, wherein the nucleotides of the segments of 2 or more nucleotides are 2'-substituted ribonucleotides.
27. (Cancelled Herewith) ~~The method according to claim 25, wherein the nucleotides of the segments of 2 or more nucleotides are 2'-substituted ribonucleotides.~~
28. The method according to claim 26, wherein the 2'-substituted nucleotides are substituted at their 2' position with methoxy or methoxyethoxy.
29. (Cancelled Herewith) ~~The method according to claim 27, wherein the 2'-substituted nucleotides are substituted at their 2' position with methoxy or methoxyethoxy.~~

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REMARKS

1 PRELIMINARY

Claims 1-29 are pending in the application with claims 1, 5, and 10 being independent. Applicants respectfully request entry of the after-final amendment submitted herewith. After entry of the amendment, claims 1-13, 16-20, 22, 24, 26 and 28 will be pending in the application. Claims 1, 5, 10 and 16-20 are amended herewith. Support for the amendments may be found in the specification as originally filed. The amendment submitted herewith places the application in better condition for appeal. The amendment does not introduce new matter.

2 REJECTIONS

A) Obviouness-type Double Patenting Rejection of Claims 1-29

Applicants acknowledge the outstanding provisional rejection of claims 1-29 for obviousness-type double patenting. Applicants restate that consideration would be given to the possibility of filing a Terminal Disclaimer in the instant application upon receiving notice that claimed subject matter is allowed.

B) The Rejection of Claim 10 Under 35 U.S.C. § 102(b) Should Be Withdrawn In View of Applicants' Comments

Claim 10 stands rejected under 35 U.S.C. § 102(b) as being anticipated by WO 93/20238 (herein after the '238 reference). Applicants traverse this rejection.

A proper reference under 35 U.S.C. § 102 must place the invention into the hands of the skilled artisan. It must meet the "description" and "enabling disclosure" requirements of 35 U.S.C. § 112. This is the minimum qualitative level that a reference must meet. *In re Hoeksema*, 399 F.2d 269, 273, 158 USPQ 596, 600 (CCPA 1968); *In re LeGrice*, 301 F.2d 929, 936, 133 USPQ 365, 372 (CCPA 1962). Moreover, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either

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expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Applicants aver that the cited '238 reference is inappropriate art under 35 U.S.C. § 102(b), and as such it cannot be used as the basis for such a rejection. More specifically, the '238 reference does not provide an enabling disclosure commensurate with the requirements of 35 U.S.C. § 112, first paragraph. The '238 reference only provides a vague reference to the possibility of using antisense technology to regulate the expression of MDM2. The '238 reference provides no direction or examples demonstrating the claimed method. There is no teaching in the reference related to the selection of MDM2 antisense oligonucleotides, no teaching in the reference relating to a mode of synthesis of MDM2 antisense oligonucleotides, no teaching in the reference related to *in vitro* delivery of MDM2 antisense oligonucleotides, and no teaching in the reference related to *in vivo* delivery of MDM2 antisense oligonucleotides.

In view of the shortcomings of the '238 reference, Applicants respectfully request reconsideration and withdrawal of the outstanding rejection.

C) The Rejection of Claims 10 and 11 Under 35 U.S.C. § 102(b) Should Be Withdrawn In View of Applicants' Comments and Amendment

Claims 10 and 11 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Kondo *et al.* (herein after Kondo). Applicants traverse the rejection of claims 10 and 11 as being anticipated by the Kondo reference.

Applicants maintain that the Kondo reference is not anticipatory of claim 10 as originally filed because it does not specifically teach that p53 is increased in cells treated with MDM2 antisense oligonucleotides. As indicated in the prior response (dated January 14, 2002), the Kondo reference teaches away from Applicants' claimed invention by indicating that p53 is not increased in cells treated with MDM2 antisense oligonucleotides.

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With the amendment submitted herewith for the sole purpose of promoting prosecution, the Kondo reference is no longer an appropriate reference under 35 U.S.C. § 102(b) because it does not specifically disclose all of the elements of the claimed invention. More specifically, the Kondo reference does not disclose the specific nucleotide sequences to which Applicants' claims are directed.

Applicants respectfully request reconsideration and withdrawal of the outstanding rejection in view of the amendment submitted herewith.

D) The Rejection of Claims 10-12 Under 35 U.S.C. § 103(a) Should Be Withdrawn In View of Applicants' Comments and Amendment

Claims 10-12 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kondo *et al.* in view of Clark *et al.* Applicants traverse this rejection.

The legal determination under 35 U.S.C. § 103 is whether the claimed invention as a whole would have been obvious to a person of ordinary skill in the art at the time the invention was made. *In re O'Farrell*, 853 F.2d 894, 902, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988). To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Obviousness cannot be established by hindsight combination to produce the claimed invention. *In re Gorman*, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed.Cir.1991).

The Office Action relies on Kondo *et al.* for disclosing the administration of MDM2 antisense oligonucleotides to cells, wherein the cells were also treated with cisplatin, a DNA damaging agent. The Office Action relies on Clark *et al.* for disclosing

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the administration of camptothecin in the treatment of pancreatic cancer. The Office Action concludes that it would have been obvious to one of ordinary skill in the art to use camptothecin, in lieu of cisplatin, in the methods of Kondo, since both agents are recognized to be DNA damaging agents and thus may be used interchangeably.

Applicants strongly object to these bases of the rejection. Applicants previously argued that Kondo *et al.* could not anticipate the claimed invention because the cited reference taught that the treatment of cells with MDM2 antisense resulted in no increase in the level of p53. The Office Action mailed April 18, 2002 responded by stating that Kondo *et al.* showed that the application of MDM2 antisense oligonucleotides did not increase the expression of p53 in cisplatin treated cells (page 3), but that this did not preclude said antisense oligonucleotides from increasing the p53 expression in untreated cells.

Applicants reiterate that obviousness cannot be established by hindsight combination to produce the claimed invention. *In re Gorman*, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed.Cir.1991). It is the prior art itself, and not the Applicants' achievement, that must establish the obviousness of the combination. Either alone or in combination, Kondo *et al.* and Clark *et al.* do not disclose that MDM2 antisense treatment results in an increase in p53 expression. The indication in the April 18, 2002 Office action that an increase in p53 expression was not precluded in untreated cells must, therefore, have come from Applicants' disclosure. Thus, the rejection under 35 § 103 on this basis is inappropriate.

Applicants also reject the assertion in said Office Action that cisplatin and camptothecin would be interchangeable because both are DNA damaging agents. Applicants respectfully point out that these two compounds operate by very different mechanisms. Camptothecin is a DNA topoisomerase 1 inhibitor, whereas cisplatin is an alkylating agent that forms adducts directly with DNA. Thus, cisplatin may be characterized as a DNA damaging agent but camptothecin cannot, since its direct target is the protein DNA topoisomerase.

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The Office Action provides no basis for the interchangeability of these compounds, it merely makes an assumption with no basis for a reasonable expectation of success. The Examiner is directed to the attached Appendix A, which is an abstract of a review on cisplatin (Trimmer E. E. and Essigmann, J.M., *Essays Biochem* 34:191-211 (1999)). The abstract points to large differences in the efficacy of cis and trans isomers of cisplatin for the treatment of cancer. Thus, a probability of success cannot be assured even with compounds that are simply cis and trans isomers of one another.

Applicants respectfully request reconsideration and withdrawal of the outstanding rejection in view of the amendment and comments submitted herewith.

E) The Rejection of Claims 1-29 Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn In View of Applicants' Comments

Claims 1-29 are rejected under U.S.C. § 112, first paragraph. The Office Action states that the specification as filed does not enable the scope of claims 1-29. The Office Action does indicate that *in vitro* and *in vivo* methods of the invention are enabled for SEQ ID NOS:28 and 47.

Applicants respectfully traverse this rejection. In *In re Goffe*, 542 F.2d 564, 191 USPQ 429, 431 (CCPA 1976), the court stated,

“[T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what has found will work or to materials which meet the guidelines specified for “preferred” materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.”

Thus, contrary to what the Office Action indicates, Applicants are not required to provide an enabling disclosure for each and every embodiment of the invention.

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In order to further prosecution, Applicants' claims are now limited by specific nucleotide sequences. Applicants aver that the amended claims are completely enabled by the specification as originally filed.

In view of the amendment and remarks, Applicants respectfully request withdrawal of the outstanding rejection.

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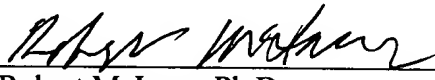
CONCLUSIONS

It is believed that all of the objections and rejections raised in the outstanding Office Action have been addressed, and the remarks provided herewith have resolved all out-standing issues in the prosecution of the captioned application. Applicants respectfully request allowance of the currently pending claims.

No additional fees are believed to be due in connection with this communication. However, please apply any additional charges, or credit any overpayment, to Deposit Account No. 50-2285. If the Examiner is of the opinion that a telephone conference would expedite prosecution of the captioned application, the Examiner is encouraged to contact Applicants' undersigned representative.

Respectfully submitted,

Dated: 4/22/03


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